Functional Ecology

British Ecological Society

*Functional Ecology* 2016 doi: 10.1111/1365-2435.12645

REVIEW

# Heterogeneity in pathogen transmission: mechanisms and methodology

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## Summary

**1.** Heterogeneity in the ability of hosts to transmit pathogens is among the most fundamental concepts in disease dynamics and has major implications for disease control strategies.
**2.** The number of secondary infections produced by an infected individual is a function of three components: an individual's infectiousness, the rate at which it contacts susceptible individuals and the duration of infection. Individual-level variation can emerge in each of these components through a combination of behavioural and physiological mechanisms.
**3.** In this review, we describe mechanisms that promote variation in the number of individuals to which an individual transmits a pathogen, emphasizing insights that can be gained by understanding which components of transmission (infectiousness, contact rate, infection duration) are primarily affected. We also discuss how behavioural and physiological processes generate transmission heterogeneities across multiple scales, from individual-level variation to heterogeneity among species.
**4.** Strategies for quantifying each transmission component are presented, and we discuss why studies focusing on only one component of the infection process may be misleading.
**5.** To conclude, we describe how future research focusing on variation in transmission across all three components can provide a more holistic view of heterogeneity in pathogen transmission.

**Key-words:** animal behaviour, disease ecology, immune responses, pathogen transmission, social networks

## Introduction

Heterogeneity in infectious disease dynamics, where most individuals infect only a few others while a small subset of the population is responsible for the majority of new cases, is common-place (Woolhouse *et al.* 1997; Lloyd-Smith *et al.* 2005). The classic example of this is Typhoid Mary, who was responsible for 28 outbreaks of typhoid fever in the early 20th century (Hudson, Perkins & Cattadori 2008), but there is evidence for 'super-spreaders' in many other human and animal disease outbreaks (Lloyd-Smith *et al.* 2005; Brooks-Pollock, Roberts & Keeling 2014). In addition, macroparasites such as helminths and arthropods are commonly aggregated in host populations, with a majority of the parasite population concentrated into a small fraction of the host population (Wilson *et al.* 2002). Indeed, across a range of both microparasites and macroparasites, the 20–80 rule refers to the general pattern where 20% of hosts contribute to around 80% of the transmission potential of a pathogen (Woolhouse *et al.* 1997). Importantly, heterogeneities in the ability of individuals to transmit pathogens, whether microparasite or macroparasite, are likely driven by a common set of mechanisms across populations. Because this phenomenon has key implications for infectious disease dynamics and control (Wilson *et al.* 2002; Keeling & Eames 2005; Lloyd-Smith *et al.* 2005; Tildesley *et al.* 2010; Ames *et al.* 2011), understanding the causes of heterogeneity in pathogen infection patterns has emerged as an important research frontier in both epidemiology and disease ecology (Stein 2011; Paull *et al.* 2012; Gervasi *et al.* 2015).

The ability of microparasites to spread in a population is commonly summarized by the basic reproduction number, $R_0$, defined as the mean number of secondary cases produced by a single initial case in a naive population

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(Anderson & May 1991). $R_0$ also describes the transmission potential of macroparasites, and in this case, is defined as the average number of female offspring produced during the lifetime of a single parasite that survives to reproduce (Anderson & May 1991). For a pathogen to invade and spread, $R_0$ must be greater than one. Thus, effective pathogen control strategies aim to reduce $R_0$ to below one. In traditional microparasite models, $R_0$ is defined as a population average and does not account for the fact that the number of secondary cases produced by an individual may vary. However, the proportion of the population that must be covered by control measures in order to achieve a sufficient reduction in $R_0$ is higher when the population exhibits heterogeneity in contact patterns than when random-mixing is assumed. To add realism, Lloyd-Smith *et al.* (2005) defined an individual's reproduction number, $V$, as the number of new infections produced by a particular individual. In a population, $V$ is distributed around the population mean, $R_0$, and super-spreading individuals can be considered individuals that fall into the extreme right tail of this distribution (Lloyd-Smith *et al.* 2005). A primary implication of heterogeneity in $V$ is that pathogens are less likely to invade a population, but outbreaks have the potential to be explosive if key individuals become infected (Lloyd-Smith *et al.* 2005). Measures targeted at this highly infectious subset can lead to more effective and efficient control strategies than population-wide measures (Woolhouse *et al.* 1997; Lloyd-Smith *et al.* 2005).

Although targeted control strategies are potentially a very effective tool for managing disease (Woolhouse *et al.* 1997; Craft & Caillaud 2011; Rushmore *et al.* 2014), such strategies are not currently feasible for many human or animal populations because logistical and diagnostic limitations make it difficult to identify super-spreaders. These limitations necessitate the development of new tools and approaches to identify key individuals, and the best method for doing this will depend on the mechanisms that give rise to heterogeneity. While much attention has been paid to heterogeneities in contact rates (Godfrey 2013; Craft 2015), the number of new infections caused by an individual ($V$) depends on more than contact alone (Box 1). In this review, we use the individual reproduction number as a framework for exploring the diversity of factors that influence the number of new infections produced by an individual via effects on three distinct parameters: contact rate, infectiousness and duration of infection. We focus on the role of physiology and behaviour in shaping heterogeneity, and highlight common and sometimes unexpected ways in which these mechanisms interact. We also discuss how these mechanisms can drive heterogeneities at multiple scales, from individuals to species. We conclude by highlighting techniques and approaches that allow for more holistic quantification of heterogeneities in natural populations, and important areas for future research. Although the concept of $V$ was conceived for microparasites, the basic principle also applies to macroparasites; our discussion is therefore relevant to all parasite types.

## Mechanisms promoting heterogeneity

Individual-level heterogeneity in $V$ can arise from multiple processes, which can be subdivided into physiological and behavioural mechanisms. This dichotomy is somewhat arbitrary and by no means mutually exclusive. Nonetheless, it is a useful dichotomy because behaviour and physiology tend to affect different components of $V$ (Box 1). Behavioural differences will typically affect $V$ through variation in contact rates, while physiological differences influence infectiousness (i.e. magnitude of pathogen shedding) and the duration of the infectious period (i.e. mortality and recovery rates). There are also interesting interactions that may simultaneously affect both behavioural and physiological outcomes.

### PHYSIOLOGY

Physiological mechanisms can lead to heterogeneity in $V$ either by creating variation in individual infectiousness or by generating variation in the infectious period. The former alters transmissibility of a pathogen while the latter alters the number of infectious contacts that an infected individual may have with susceptible individuals. Both of these have important implications for disease spread. One way to conceptualize how physiology contributes to heterogeneity in $V$ is by considering the impact of physiological processes on host defences. Physiological mechanisms influence the specific defence strategies hosts adopt towards pathogens. In some cases, a host might resist a pathogen by reducing the pathogen's growth; in others, a host might tolerate the pathogen by limiting the damage caused rather than the pathogen's growth or proliferation (Simms 2000; Råberg, Graham & Read 2009). Resistance is typically a function of the host's immune system, whereas tolerance may be elicited by immune components as well as a variety of other physiological factors (Mednhitov, Schneider & Soares 2012). With respect to heterogeneities in $V$, the difference between adopting a resistance vs. tolerance strategy has profound implications for host infectiousness. All else being equal, a resistant host will be less infectious than a tolerant one because the resistant host actively controls its pathogen burden while the tolerant host does not. Empirical studies on domestic and free-ranging animals suggest that resistance and tolerance strategies to the same parasites can co-occur both within populations and individuals (Bisset *et al.* 2001; Hayward *et al.* 2014). If this is the case, then physiological factors that determine the degree of variation in relative investment in resistance vs. tolerance may generate strong between-individual variation in infectiousness.

A key physiological trait that influences host investment in pathogen defence is body condition. The effects of condition on host immunological responses are well described

**Box 1**
**Decomposing V**

Two primary pathways give rise to heterogeneity in $V$ (Fig. A): variation in number of contacts and variation in the likelihood of transmitting an infection given contact. First, an animal may be a super-spreader because it has a greater overall number of encounters during which transmission may occur. Total number of encounters experienced by an infected animal will be determined by the rate at which contacts occur and the total length of time in which the animal is capable of infecting others (infectious period). Mortality and recovery rates both act to determine the infectious period, and these rates are heavily influenced by physiological processes. Thus, both physiological and behavioural factors determine the total number of encounters.

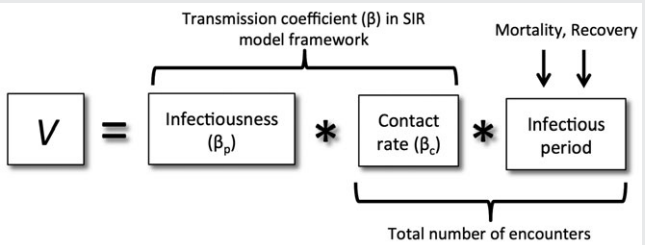



**Fig. A.** Components contributing to variation in the number of secondary infections produced by an infected individual, or $V$.

Secondly, an animal may be a super-spreader because it is highly infectious. Given an equal number of encounters, a more infectious animal has a higher likelihood of transmitting a pathogen. For example, so-called 'super-shedders,' which are individuals that shed above average numbers of infective agents into their environment, are more likely to infect others. Super-shedding has sometimes been considered distinct from super-spreading in that super-spreading refers specifically to behavioural, contact-related mechanisms (Chase-Topping *et al.* 2008). This division perhaps emerged because of a much longer history of research on parasite aggregation and the highly skewed distributions characteristic of macroparasite infection intensities (Crofton 1971; Shaw, Grenfell & Dobson 1998; Wilson *et al.* 2002). We emphasize that super-spreading should be defined as any situation where a minority of individuals are responsible for a disproportionate amount of transmission, and that super-shedding can be considered a special case of super-spreading. The concept of $V$ unifies both super-shedding and behavioural super-spreading within a common framework.

The rate at which infected individuals transmit infections to susceptible individuals is usually referred to as the transmission coefficient and denoted as ß (Anderson & May 1991). This parameter combines aspects of both encounter rate and infectiousness, and thus may obscure the root source of heterogeneity in individual transmission rates. To address this, ß can be decomposed into two primary components that reflect the rate at which an infected animal transmits to susceptible animals (Dobson 1995). To transmit an infection, an individual must first contact a susceptible individual (behavioural component of transmission, $ß_c$). Once an encounter between an infected and susceptible individual has occurred, the probability that the susceptible individual becomes infected depends on the efficiency of transmission, or transmissibility (Bansal, Grenfell & Meyers 2007; Craft *et al.* 2010). This physiological component of transmission ($ß_p$) relies on both the infectiousness of the infected host and the susceptibility of the susceptible host (Hawley *et al.* 2011). Sometimes there may also be covariation between $ß_p$ and $ß_c$, which is reviewed in detail elsewhere (Hawley *et al.* 2011).

in the literature (Beldomenico & Begon 2010). Factors that depress host condition, such as poor nutrition, can increase infectiousness by relaxing the level of opposition to pathogen survival and proliferation within the host (Cornet *et al.* 2014). In direct contrast, better host nutrition can also increase pathogen shedding, for instance, by augmenting the resources available for pathogen growth, as has been hypothesized for *Pasteuria ramosa* infection in *Daphnia* (Vale, Choisy & Little 2013). In fact, well-fed *Daphnia* not only have more parasites than poorly fed individuals, but parasites are more aggregated among well-fed populations suggesting that more food can increase the potential for super-spreading (Vale, Choisy & Little 2013). Accumulating evidence suggests that good and poor condition hosts often respond differently to infection. For example, instead of having overall high vs. low immune responses, hosts in these different categories might partition their investment in immunity in different ways (Gilot-Fromont *et al.* 2012). Under some circumstances, changes in condition might promote an overall shift in defence strategy; poor condition hosts might invest more in immunological resistance, while good condition hosts mount weaker immune responses, effectively tolerating rather than resisting the pathogen (Budischak *et al.* 2015). As with the food-mediated increase in pathogen growth observed in *Daphnia*, a bias in pathogen defence towards tolerance or resistance in good and poor condition hosts, respectively, could lead to the counterintuitive pattern

where high nutrition and good condition are associated with higher super-spreading potential.

Coinfection by multiple pathogens can also play a significant role in generating heterogeneity, and these effects are largely driven by pathogen-induced changes in host physiology. It is well known that infection by one pathogen can modify the likelihood of secondary infections (Telfer *et al*. 2010; Henning *et al*. 2014), but coinfection can also generate heterogeneity in infectiousness and infection duration. For example, when human nasal carriers of *Staphylococcus aureus* are coinfected with mild respiratory viruses, they become *S. aureus* super-shedders or 'cloud patients' who are surrounded by clouds of aerosolized bacteria (Bassetti *et al*. 2005). A similar phenomenon may have been responsible for several SARS super-spreading events (Bassetti, Bischoff & Sherertz 2005). Similarly, laboratory mice coinfected with bacteria such as *Bordetella bronchiseptica* and *Mycobacterium bovis* can become helminth super-shedders, releasing 3·5 to 4 times more worm eggs than non-coinfected conspecifics (Lass *et al*. 2012; Budischak *et al*. 2015). Helminths also have reciprocal effects on microparasites owing to their strong modulatory effects on host immune function (Salgame, Yap & Gause 2013). In African buffalo (*Syncerus caffer*), for instance, helminth infection suppresses antimicrobial immunity (Ezenwa *et al*. 2010), and individuals who are coinfected with helminths and bovine tuberculosis die faster, suggesting that helminth coinfection truncates the infectious period of TB (Ezenwa & Jolles 2015). The synergistic mortality in helminth-TB coinfected animals is likely driven by a combination of immunological and condition effects (Jolles *et al*. 2008).

Physiological factors can also create heterogeneities in vector-borne disease systems. For example, the attractiveness of hosts to vectors can be influenced by host physiological traits such as odour, body mass and body heat (Allan 2010; Takken & Verhulst 2013). The African malaria mosquito, *Anopheles gambiae*, for instance, responds strongly to human skin odours. Human body odour is correlated with the composition of skin microorganisms, and people that are highly attractive to *A. gambiae* have a higher abundance and lower diversity of bacteria on their skin (Verhulst *et al*. 2011). Importantly, highly attractive individuals are not only more likely to acquire new infections from vectors, but also to pass on pathogens to subsequent vectors with whom they come into in contact. Thus, such individuals are simultaneously super-receivers (i.e. significantly more likely to acquire a pathogen than the general population) as well as super-spreaders. For malaria, there is also evidence that hosts who are already infected with *Plasmodium* parasites become more attractive to mosquitoes (Lacroix *et al*. 2005; Cornet *et al*. 2013; de Moreas *et al*. 2014). In mice, elevated volatile emission during infection with *P. chabaudii* has been linked to enhanced host attractiveness to *A. stephensi* mosquitoes (de Moreas *et al*. 2014). Interestingly, the increased release of volatiles by infected hosts coincides with a critical period when mice are highly infectious, lending support to the idea that differential vector attraction may generate inter-individual heterogeneity in the rate at which different hosts infect vectors. Understanding the impact of such variation on vector-borne disease dynamics is an important research frontier (Smith *et al*. 2014).

## BEHAVIOUR

The primary means by which behaviour directly affects $V$ is through contact rates among individuals or other sources of infection (e.g. contaminated food or habitat, infected vectors, etc.). In particular, the role of behaviour in shaping between-host contact and its consequences for the transmission of directly transmitted pathogens has garnered considerable attention in the literature. We know that individuals vary in the numbers of contacts in which they engage, either because of population density (Keeling & Rohani 2008) or the size of their social group (Patterson & Ruckstuhl 2013). However, population- or group-level metrics of contact do not capture the full scope of heterogeneity in contact rates. More recently, social network analysis has been used to describe individual variation in contact patterns and to translate individual-level heterogeneity to the structure of contacts at the population scale (Godfrey 2013; Craft 2015). Individual variation can be quantified by a number of centrality metrics, which include measures of the strength and diversity of an individual's contacts. Individual contact patterns can be measured not only from direct contacts within the network, but also from indirect connections, and these sort of second-order contacts capture aspects of overall network structure that can substantially impact the dynamics of an epidemic (Box 2).

Real-world networks often exhibit extreme heterogeneity in the number of contacts in which individuals engage (Godfrey 2013; Rushmore *et al*. 2013), and it is often assumed that individuals with many contacts can transmit a pathogen more widely (Craft 2015). Many studies show that social network position is highly correlated with the risk of acquiring infections (Drewe 2009; Fenner, Godfrey & Bull 2011; MacIntosh *et al*. 2012; VanderWaal *et al*. 2013; Rimbach *et al*. 2015). In group-living meerkats (*Suricata suricatta*), for example, certain types of interactions, such as grooming conspecifics or visiting other social groups, were correlated with risk of *Mycobacterium bovis* infection, and individuals varied in how often they engaged in these interactions based on sex and social status. Subordinate meerkats tended to engage in grooming others more frequently; thus, transmission chains could potentially be disrupted through interventions targeting this subset of animals (Drewe 2009; Drewe *et al*. 2011). However, while it is relatively easy to correlate the risk of acquiring an infection with behaviour, it is often difficult to empirically assess the importance of network position for $V$ because who transmitted to whom is typically unknown. In

**Box 2**
**Social networks, cutpoints and transmission potential**

In contrast to super-spreaders whose importance stems from having a large number of connections in their social network, individuals may also be disproportionately important in the spread of pathogens if they occupy key positions in their network that, if disrupted, hinders dissemination of pathogens across different subgroups (Salathé & Jones 2010; VanderWaal *et al.* 2014b; Nunn *et al.* 2015). The critical point here is that these individuals are not necessarily important because they have high $V$ directly, but because they can serve as bottlenecks for pathogen flow. Their infection may lead to a cascade of new infections by providing the pathogen access to a new area of the network. Targeting such individuals may fracture the connectivity of the population. These individuals can be designated 'cutpoints' because their removal may fragment the population in such a way as to prevent the pathogen spread. Targeted interventions at cutpoints have the potential to increase the overall level of clustering in the population, and theoretical models suggest that this can hinder the spread of disease (Newman 2003; Badham & Stocker 2010; Salathé & Jones 2010; Ames *et al.* 2011). To illustrate, we simulated a hypothetical epidemic in a giraffe social network. The epidemic curve shows that the pathogen initially spreads rapidly in the upper cluster of individuals (green dots), then the number of new cases slows (Fig. B). The growth rate of the epidemic does not increase again until after the cutpoint individuals are infected, allowing the pathogen to spread to a new part of the network (lower cluster, blue dots).

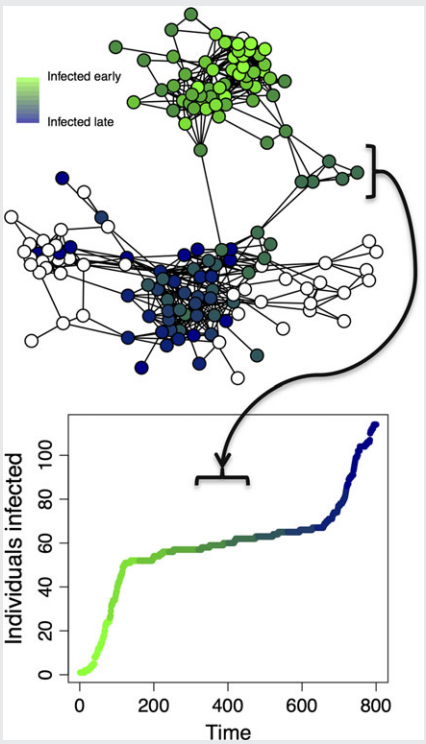



**Fig. B.** Using data from (VanderWaal *et al.* 2014c), the spread of a pathogen within a giraffe social network was simulated using a Susceptible-Infected (SI) compartmental model. The epidemic was seeded within the top cluster of the network, and the time step in which each individual became infected was recorded. Lighter green to dark blue colours indicate individuals infected early to late in the epidemic, respectively. The cumulative number of individuals infected over time was plotted as an epidemic curve (bottom panel).

The concept of cutpoints is intimately related to $V$. Although cutpoints may not have high $V$ when compared to $V$'s overall distribution over the entire time course an epidemic, a cutpoint may have high $V$ in certain critical time steps if we compare $V$s within a restricted timeframe. Using the number of susceptible contacts as a proxy for $V$ in our example, the potential contacts that could be infected by each cutpoint over the entire time period was fewer than five animals, which is not particularly high when compared to the overall distribution of $V$. However, from time step $t$ = 200–400, only cutpoints had contact with significant numbers of susceptible individuals, and thus were responsible for maintaining transmission during this critical window (see Fig. S1, Supporting information). For this reason, cutpoints can be considered an important type of super-spreader. By examining the distribution of $V$ in a temporally dynamic fashion the cutpoint concept adds a temporal dimension to quantifying heterogeneities in $V$.

addition, if contact patterns change as a consequence of sickness behaviours (Hawley *et al.* 2011), then an individual's risk of acquiring vs. likelihood of transmitting an infection will not necessarily be correlated. Nonetheless, epidemiological models have demonstrated that population-wide spread of disease is more extensive if highly central nodes in the network are infected early during an epidemic (Lloyd-Smith *et al.* 2005; Rushmore *et al.* 2014).

In the absence of data on who transmitted to whom, the ramifications of variation in contact rates and social network position can be examined using epidemiological models to simulate the size of epidemics originating from individuals with varying levels of network connectivity (Craft & Caillaud 2011; Craft 2015). In chimpanzees (*Pan troglodytes*), models demonstrate that a greater proportion of the population becomes infected when epidemics originate in individuals with large numbers of direct contacts (Rushmore *et al.* 2014). Variation in contact degree and network position is reliant on the chimpanzee's complex social system emerging from kinship relationships, dominance hierarchies and ranging behaviour (Rushmore *et al.* 2013). However, it is clear that complex network structures and large variations in individual contact rates can emerge even in relatively simplistic social systems due to variation in factors such as mating behaviour and personality (Thrall, Antonovics & Dobson 2000; Dizney & Dearing 2013).

Animal personality, sometimes referred to as temperament (Carere & Maestripieri 2013), can influence patterns of infection for a variety of pathogen types, ranging from directly transmitted microparasites to environmentally or trophically transmitted macroparasites. Personality has major effects on individual space use, contact rates, risk avoidance and activity levels, all of which can alter pathogen transmission opportunities (Boyer *et al.* 2010; Koprivnikar, Gibson & Redfern 2012; Dizney & Dearing 2013). For example, bold individuals are less averse to risk and may engage in more exploratory behaviour compared to shyer individuals (Carere & Maestripieri 2013). These types of behaviours modify an individual's contact rate with other individuals, as well as contact with infectious agents in the environment. Personality traits can also alter where animals shed infectious agents in the environment. Bold deer mice (*Peromyscus maniculatus*), for instance, are not only in contact with conspecifics more frequently, but they are also three times as likely to be infected by hantavirus (Dizney & Dearing 2013). Boldness may also relate to intraspecific aggression, which has been linked to hantavirus transmission (Glass *et al.* 1988). Taken together, this suggests that bold individuals may be both more likely to acquire and to transmit the virus to conspecifics. An interesting line of future research is how personality affects interspecific transmission. In the case of hantavirus, behaviours associated with boldness, such as exploratory and risk-taking behaviours, may increase the likelihood of zoonotic transmission of hantavirus from rodents to humans if bold animals enter human households more readily. Behavioural patterns are also important for environmentally transmitted pathogens when patterns of space use and habitat choice affect the number of individuals that hosts contact in space. For example, boldness affected tick levels in chipmunks (*Tamias sibiticus*) by increasing space use and exposure to ticks (Boyer *et al.* 2010). Such variation in the acquisition of pathogens and vectors creates positive correlations in the likelihood of initial infection (super-receiving) and subsequent transmission to other hosts (super-spreading)(Adelman *et al.* 2015).

## INTERACTIONS BETWEEN BEHAVIOUR AND PHYSIOLOGY

Physiology and behaviour are intimately connected; physiological mechanisms can mediate behaviour, and behaviour can affect an animal's physiological state. Stress is perhaps one of the best examples of this type of interaction. Chronic stress has direct effects on the immune system by impairing both cell-mediated and humoural immune responses, and as such, can impact the duration of infection (Glaser & Kiecolt-Glaser 2005). Stress can also indirectly increase host infectiousness because cortisol and epinephrine, two hormones associated with stress in mammals, can increase mucous secretion, vasodilation, and symptoms such as sneezing (Cohen *et al.* 1997). Therefore, variation across individuals in their exposure and response to stress likely promotes heterogeneity in *V*. Behaviour, particularly social behaviour, is an important driver of variability in responses to stress in both humans and animals (Sapolsky 2004, 2005). Social dominance, for instance, has been linked to stress and parasitism in several mammals, though the direction of the effect differs among species and contexts. In some cases, dominant individuals experience more stress and parasitism, and in others, the reverse is true (Creel 2001; Muehlenbein 2006; Ungerfeld & Correa 2008). A recent meta-analysis showed that immune function did not consistently differ between high and low ranking males, but dominant males tended to be more highly parasitized (Habig & Archie 2015). Relationships between stress and pathogen shedding can also be affected by animal personality and social context (Capitanio *et al.* 2008). Thus, behavioural-induced variation in responses to stress could determine which animals are more prone to infection, more likely to become super-spreaders, or to succumb to disease. Importantly, an animal's stress response can also feedback on its behaviour. As a compelling example of this, Setchell *et al.* (2010) found that the relationship between dominance rank and stress changed direction depending on the stability of the dominance hierarchy in male mandrills (*Mandrillus sphinx*), and that males with higher stress levels were infected with a greater variety of gastrointestinal parasite taxa. Considered in the context of transmission heterogeneities, interactions between stress and behaviour have the potential to impact all components of *V*, from increasing or decreasing contact rates to altering infectiousness, recovery and mortality.

Reproduction is another key area where interactions between physiology and behaviour can drive heterogeneities in $V$. Physiological changes associated with reproduction, such as changes in the secretion of gonadal hormones, are known to have important immunomodulatory effects. In females, elevated levels of progesterone during pregnancy inhibit humoural immunity, while oestrogens stimulate humoural immunity (Tait, Butts & Sternberg 2008). In males, elevated testosterone levels are often associated with less robust immune responses (Roberts & Peters 2009; Edler *et al.* 2011). Thus, hormone-mediate changes in immunity and immunosuppressive effects of testosterone might underlie common male-biases in infection patterns, such as increased parasite susceptibility, infection duration, shedding (Zuk & McKean 1996; Hughes & Randolph 2001; Luong *et al.* 2010) and even elevated parasite-induced mortality (Moore & Wilson 2001). In almost all animals, the physiological changes associated with reproduction are also accompanied by behavioural changes that have consequences for $V$. During reproduction, males of many species alter their behaviour in ways that enhance their ability to find or attract females. In addition to suppressing immune function, variation in testosterone levels may alter male contact rates, activity patterns, space use and home range size, which may enhance or reduce opportunities for pathogen transmission (Grear, Perkins & Hudson 2009; Edler *et al.* 2011; Fuxjager *et al.* 2011).

A third area where physiological and behavioural mechanisms combine to influence $V$ is sickness behaviour. Sickness behaviours are an integral part of inflammatory responses to infection, and typically involve reductions in food intake, social activity, sexual behaviour and other core activities (Hart 1988; Dantzer & Kelley 2007). These behaviours may help hosts fight infection by shunting energy away from non-essential activities and towards the immune system (Hart 1988). However, the degree to which animals invest in sickness behaviours can vary considerably with social, ecological, and life-history context (Adelman & Martin 2009; Lopes 2014). For example, in the presence of conspecifics, zebra finches showed a marked reduction in sickness behaviour after an immune challenge in comparison to individuals that were kept in isolation (Lopes *et al.* 2012). Since both singly and socially housed birds showed increased levels of pro-inflammatory cytokine responses to the immune challenge, these results suggest that social birds modulated their sickness behaviours independently of changes in physiology. This type of context-dependent reduction in sickness behaviour could prolong recovery or increase pathogen-induced mortality, both of which can create variation in the infectious period. Sickness behaviours can also generate heterogeneity in contact rates. In the simplest case, reductions in activity that accompany infection might reduce contact rates between infected individuals and conspecifics (Hart 1988), and individual variation in the expression of sickness behaviours would lead to variation in contact patterns. Counter-intuitively, sickness behaviour may also increase contact rates in some instances. For example, one of the consequences of *Mycoplasma gallispeticum* infection in male house finches is reduced aggression, and healthy males may increase the time they spend feeding near these less-aggressive, infected males (Bouwman & Hawley 2010). In this case, the sickness behaviour of infected males, coupled with the behaviour of healthy males, increases contact rates between infected and uninfected individuals and enhances the super-spreading potential of infected males.

Finally, considering pathogen defences holistically suggests another key way in which behavioural and physiological mechanisms might interact to influence $V$. Both behaviour and physiology contribute to pathogen defence (Hart 1990), and there are some recent indications that individuals may trade-off between behavioural and physiological defences. In Galapagos finches (*Geospiza* spp.), for example, individuals that spend more time at feeders (i.e., low investment in behavioural avoidance of pathogens) invest more in immune defences (Zylberberg 2014). Further, individual passerines may balance behavioural and immune defences during the course of a single day, perhaps adaptively re-allocating immune investment as a response to low-risk or high-risk behaviours for pathogen exposure (Zylberberg 2015). How these trade-offs impact $V$, as well as the implications for population-level transmission dynamics, is a potentially fascinating area of research yet to be fully explored.

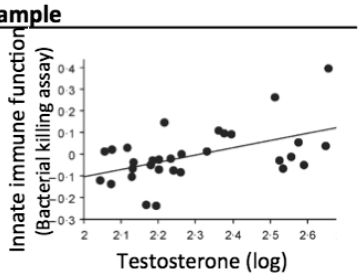
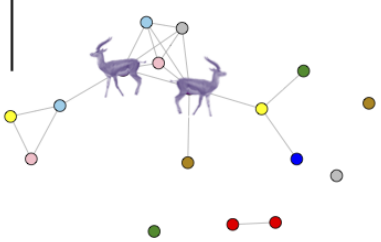
Regardless of whether a mechanism promotes heterogeneity in $V$ via behaviour, physiology or a combination of the two, if it increases both the likelihood of acquiring and transmitting a pathogen, a situation is created where an individual is both a super-receiver and super-spreader. For example, individuals with high contact rates may experience more transmission opportunities allowing them to both receive and, in the absence of sickness behaviours, pass on directly transmitted pathogens (Adelman *et al.* 2015). Similarly, a compromised immune system may affect both defence against initial acquisition of pathogens and control of pathogen proliferation and subsequent shedding. Although much more attention has been placed on understanding super-spreading in the literature, it is important to note that correlations between super-spreading and -receiving can have multiplicative effects on $R_0$ (Woolhouse *et al.* 1998).

## Scales of heterogeneity

The behavioural and physiological mechanisms described above can generate heterogeneities not only at the level of an individual host, but also at higher scales, such as across classes of individuals (e.g. by sex or reproductive status) or host species (Table 1). At the individual level, variation in $V$ is not easily predicted from age-class or other trait, so data on each individual must often be obtained to detect

**Table 1.** Scales at which heterogeneity occurs and example sources of variation at each scale. The African antelope, Grant's gazelle (*Nanger granti*) is used as an example highlighting how these different processes may occur in the same system

| Level of Organization | Example |
|---|---|
| **Individuals**<br>*Definition and measurement*<br>- *V* cannot be approximated by basic individual attributes (e.g., age and sex)<br>- Transmission potential must be measured in each animal individually<br><br>*Possible sources of heterogeneity*<br>- Stress levels<br>- Immune function<br>- Coinfection<br>- Personality<br>- Dominance/social position<br>- Vector preferences |  <br>Individual male Grant's gazelles vary in endogenous testosterone levels, which has implications for immune function, and consequently, parasitism (Ezenwa et al. 2012). |
| **Classes of individuals**<br>*Definition and measurement*<br>- *V* can be reliably approximated from continuous variation among individuals related to an attributes or trait<br>- Transmission potential can be summarized at the class level<br><br>*Possible sources of heterogeneity*<br>- Age-correlated changes in physiology<br>- Sex differences in social behavior or space use<br>- Mating behavior<br>- Body size<br>  |  <br>Males with higher testosterone are more likely to defend territories, and territorial males as a class have physiological and behavioral attributes that affect their susceptibility to parasite infection and rates of shedding (Ezenwa 2004a; Ezenwa et al 2012). |
| **Species**<br>*Definition and measurement*<br>- *V* varies reliably between species<br>- Transmission potential can be summarized at the species level<br><br>*Possible sources of heterogeneity*<br>- Host competence<br>- Species-typical space use<br>- Species-typical social behavior<br>- Species-typical physiology<br>- Vector preferences<br><br>Grant's gazelle<br>Buffalo<br>Cattle<br>Eland<br>Giraffe<br>Hartebeest<br>Impala<br>Thomson's gazelle<br>Zebra | **At the species level,** Grant's gazelle tend to have a higher number of multi-species contacts, on average, than other species in a multi-host transmission network based on E. coli subtype sharing (VanderWaal et a. 2014).<br>  |

patterns of heterogeneity. However, at the next scale up, certain classes of individuals may have similar *V*, and transmission potential may be approximated simply by knowing a few key attributes about these individuals. At the species-level scale, the certain host species may have far higher transmission potential than others as a direct result of their physiological and behavioural attributes (Gervasi *et al.* 2015). Understanding how individual-level behavioural and physiological factors scale up to drive higher-level heterogeneities is therefore a critical part of

improving our general understanding of the 'super-spreader' phenomenon. Below, we discuss an emerging set of case studies showing that heterogeneities at higher scales can be predictable, which has direct applications for disease management and control.

## CLASSES OF INDIVIDUALS

Interventions targeted at super-spreader individuals have the potential to limit disease spread much more effectively than non-targeted control measures (Lloyd-Smith *et al*. 2005), but identifying *specific individuals* that are super-spreaders is challenging and time-consuming. Even if certain behaviours are identified as high-risk (Drewe 2009), the application of strategies targeting individual animals that display high-risk behaviour would require behavioural monitoring of the population by a trained observer. Thus, it is more efficient to identify *classes of individuals* that are super-spreaders. Importantly, control strategies that target classes of individuals within populations may be more generalizable across populations because the typical physiology or behaviours exhibited by that class are likely similar across populations. Adult males, for example, often play a crucial role in the maintenance of infectious diseases in mammal populations (Ferrari *et al*. 2003; Grear, Perkins & Hudson 2009). For example, in yellow-necked mice (*Apodemus flavicollis*), treatment of males reduced population-level prevalence of gastrointestinal helminths across both males and females, whereas treatment of females had no effect beyond the treated individual (Ferrari *et al*. 2003). Male yellow-necked mice are thought to be key hosts in this system because of sex differences in immunological responses, space use, home range overlap or contact rates (Ferrari *et al*. 2003).

Transmission rates can also exhibit strong age dependence (Grenfell & Anderson 1985; Heymann *et al*. 2004; Weycker *et al*. 2005), which can arise from age-related differences in immunological responses and contact rates. Acquired immunity is often correlated with age, and this can contribute to age-related patterns of macroparasite aggregation in which younger individuals tend to exhibit more variation in infection intensity (Grenfell *et al*. 1995; Wilson *et al*. 2002). Likewise, high contact rates among immunologically naive children at schools enhance transmission of microparasitic diseases, and control measures targeted at school children, such as vaccination or school closure, may be very effective at reducing population-wide epidemics (Heymann *et al*. 2004; Weycker *et al*. 2005). The same pattern holds in wild populations as evidenced by contact patterns exhibited in juvenile Belding's ground squirrels (*Spermophilus beldingii*). Juvenile male squirrels tended to be more exploratory than other age-classes, and colonies with more juvenile males had spatial contact networks with lower levels of clustering, a feature that was associated with higher prevalence of *Crytosporidium* parasites (VanderWaal *et al*. 2013).

Recent models of infectious disease spread in a community of chimpanzees showed that outbreak size could be reliably predicted based on the 'traits' of the index case. Epidemics that originated in individuals that displayed certain traits, such as having a large family or a home range located centrally in the community, were associated with larger outbreaks (Rushmore *et al*. 2014). Outbreak size was predictable from these trait-based approaches because traits approximated network position (Rushmore *et al*. 2013). Importantly, control measures targeted towards classes of individuals displaying high-risk traits were nearly as effective as targeted control based on individual network position (Rushmore *et al*. 2014). This work highlights the potential of using classes of individuals to approximate heterogeneity in $V$ for targeted control efforts and the need for developing a better understanding of the range of factors that shape $V$.

## HOST SPECIES

Because of interspecific variation in physiology and behaviour, certain species may function as super-spreaders for multi-host pathogens if individuals of that species tend to have higher $V$ on average. Species whose contribution to community-wide transmission is disproportionate to their relative abundance can be considered 'super-spreading species' (Paull *et al*. 2012). In a study of West Nile Virus, for example, American robins (*Turdus migratorius*) comprised over 40% of mosquito blood meals as compared to other songbird species but they accounted for <4% of the available avian hosts, making them disproportionately important in virus transmission (Kilpatrick *et al*. 2006). Vector preferences for certain host species are one mechanism for interspecific differences in transmission potential (Takken & Verhulst 2013), but heterogeneity across species in transmission potential may have behavioural and physiological bases as well.

Indeed, determining if there are specific aspects of species physiology or behaviour that are consistently correlated with higher transmission potential would have profound implications for understanding the dynamics of multi-host pathogens. Interspecific variability in transmission is strongly influenced by physiological differences in reservoir competence, which can be defined as the efficiency with which a host acquires and transmits a pathogen (Paull *et al*. 2012; Gervasi *et al*. 2015). For example, white-footed mice (*Peromyscus leucopus*) are highly competent hosts for *Borrelia burdorferi*, the causative agent of Lyme disease. One hypothesis for why these mice are highly competent hosts for *Borrelia* is related to their fast pace of life (Keesing *et al*. 2010; Huang *et al*. 2013). In general, the pace of life hypothesis posits that strategies of immune allocation in vertebrates (e.g. investment in innate vs. adaptive immune responses) vary along a slow to fast life-history continuum (Lee 2006). In a test of this hypothesis across three rodent hosts of *Borrelia* that ranged from relatively fast to relatively slow life histories, Previtali *et al*. (2012) found that white-footed mice

mounted the strongest innate bacteria killing responses but the weakest antibody responses. This result suggests that differential investment in short-term innate over long-term adaptive immunity may contribute to the high competence status of these mice. A recent broad scale analysis of rodent species also found evidence that traits associated with a fast-paced life history distinguished zoonotic disease reservoir species from non-reservoir hosts (Han *et al*. 2015). Likewise, fast-paced amphibian species were found to be more prone to infection and pathological effects of the trematode *Ribeiroia ondatrae* under experimental conditions (Johnson *et al*. 2012). If these life history-based differences reliably reflect variation in host physiology, then for some multi-host pathogen systems, a life history trait-based approach could be used to identify interspecific transmission heterogeneities and help guide control strategies.

Behaviour is another factor that can contribute to variation in transmission potential among species. For example, highly social species experience higher contact rates and more transmission opportunities, creating situations where a pathogen can rapidly proliferate within the species (Coté & Poulin 1995; Altizer *et al*. 2003) and subsequently spillover into other species. However, territoriality or infrequent contact between social groups may create conditions in which population-wide pathogen dissemination is hindered, even if within-group transmission rates are high (Loehle 1995; Altizer *et al*. 2003; Cross *et al*. 2005; Nunn *et al*. 2008, 2015). The degree to which social behaviour facilitates vs. hinders population-wide transmission depends on the insularity of social groups, and the frequency of contact between groups relative to the infectious period (Cross *et al*. 2005; Craft *et al*. 2010). Interestingly, highly social species may compensate for higher contact rates by investing more in behavioural defences against pathogens (Meunier 2015; Schaller, Murray & Bangerter 2015), and species with promiscuous mating systems may invest more heavily in immunological defences (Nunn, Gittleman & Antonovics 2000, 2003). For example, eusocial insects engage in behaviours, such as allogrooming and removal of corpses from the nest, that collectively may confer 'social immunity' to certain pathogens (Meunier 2015). More generally, antiparasite behaviours may be a major form of behaviour that can create heterogeneities in transmission potential. For example, variation in grooming rates after tick exposure among hosts of Lyme disease may strongly influence their relative contributions to the density of infected ticks in the environment (Keesing *et al*. 2009). Indeed, species that invest disproportionately in antiparasite or hygienic behaviours may act as important moderators of pathogen transmission. This is somewhat analogous to the concept of a 'dilution host,' whose presence in a host community can reduce the transmission of pathogens via a range of possible mechanisms (Keesing, Holt & Ostfeld 2006).

Moving beyond simple characteristics of social behaviour, such as grouping and territoriality, mating system and group composition can have subtle but profound effects on disease dynamics, such as altered social dynamics due to social perturbations in the group (Bielby *et al*. 2014). For example, in species with harem-based mating systems, disease-induced mortality of the harem's male can accelerate the spread of pathogens across the landscape (Nunn *et al*. 2008). Indeed, models show that Ebola virus is able to invade a wider number of social groups in gorillas (*Gorilla gorilla*) than in chimpanzees due to pathogen-mediated dispersal in gorilla harems after the death of the silverback. Conversely, the larger group sizes exhibited by chimpanzees resulted in higher overall prevalence (Nunn *et al*. 2008). Thus, specific features of social and mating behaviour that facilitate rapid, population-wide spread within a species may determine the relative risk of pathogen spillover to other susceptible species (Paull *et al*. 2012).

Finally, while sociality is the most obvious behaviour affecting contact rates in directly transmitted disease systems, other behaviours may be important for pathogens with different transmission modes. For environmentally transmitted pathogens, space use patterns may affect the total number of inter- and intraspecific contacts an animal makes, and species with large home ranges or who use a greater diversity of habitats may have the potential to disseminate pathogens more widely. For example, in African savanna systems, zebras (*Equus burchelli*) move longer distances than many other ungulates, and consequently seem to function as a 'cutpoint species' by linking regions of *Escherichia coli* transmission networks that would otherwise be poorly connected [Box 2, (VanderWaal *et al*. 2014b). Grant's gazelles, in contrast, were connected to a large number of hetero- and conspecifics in the network, demonstrating that this species was highly involved in disseminating *E. coli* locally but, unlike zebras, gazelles did not play a bridging role in the network. Cutpoint species have also been discussed in the context of reservoir dynamics, where a non-maintenance species is considered the primary intermediate host facilitating the transmission of disease from a reservoir host species and the target population of interest, such as domestic or endangered species (Caron *et al*. 2015).

## Quantifying heterogeneity

Since the introduction of $V$ in the literature by Lloyd-Smith *et al*. (2005), each component of $V$, and the mechanisms influencing these components, has typically been examined in isolation, yielding an incomplete picture of the drivers of individual heterogeneity. In some cases, there are correlations between measuring a single component and $V$; but this piecemeal approach may not provide the complete picture (but see (Perkins, Ferrari & Hudson 2008; VanderWaal *et al*. 2014b). Variation in $V$ is notoriously hard to quantify given the inherent difficulty in determining who transmits to whom and interactions between each component. For example, correlations

between infectiousness and $V$ may be obscured if susceptible contacts actively avoid highly infectious animals (Hawley *et al*. 2011). Quantifying contact rates as an index of $V$ is also plagued by the possibility that contact rates change once an animal becomes infected. Despite the complex interactions between components of $V$, efforts to quantify each dimension serve as useful starting points in quantifying heterogeneity in transmission.

### INFECTIOUS PERIOD AND INFECTIOUSNESS

While laboratory approaches are viable options for quantifying variation in infectiousness and infectious period, we focus here on how to measure these components of $V$ in natural settings. It is often more manageable to estimate an individual's relative risk for acquiring an infection in natural settings rather than quantifying its ability to clear or control a pathogen once established. Although it may be tempting to assume that an individual's risk of becoming infected might be correlated with its transmission potential, this is not necessarily the expectation for immunological processes, since innate immunity is typically responsible for preventing acquisition while adaptive immunity determines how well the host is able to control and clear the infection once acquired (Tizard 2012).

The infectious period is difficult to quantify in natural settings because the exact time of exposure is usually unknown. In addition, the regular, repeated, and often invasive sampling regime required to quantify the duration of an infection can be difficult to achieve in free-ranging populations, which makes infectious period among the most challenging components of $V$ to measure. A more tractable option may be to investigate the infectious period for pathogens where the infectious period is terminated by mortality, which is easier to observe than recovery. In such cases, life span post-infection could potentially be used as a surrogate for infectious period. Pathogens that fall into this category include chronic infections, such as bovine tuberculosis and some gastrointestinal helminths, and acute infections with very high mortality, such as rabies in most mammalian hosts and plague in prairie dogs. Uncertainties about the time of exposure can still create difficulties in quantifying the infectious period unless the onset of infection is associated with observable clinical signs (e.g. mange in wolves)(Almberg *et al*. 2015).

In natural populations, measuring infectiousness through some aspect of shedding (viral load, faecal egg counts, etc.) is relatively easier than quantifying the infectious period. An extensive body of literature on parasite aggregation has used shedding of macroparasites as an indicator of infection intensity (Wilson *et al*. 2002), and this illuminates one dimension on variation in $V$. While shedding of parasites clearly demonstrates variation in infectiousness, which likely correlates with $V$ in some fashion, it falls short of providing a full picture of variation in $V$. Nonetheless, this area of research is well developed and provides valuable insights into how to quantify heterogeneity, from general rules of thumb such as the 20–80 rule to the selection of appropriate statistical distributions to quantify $V$ (Scott 1987; Woolhouse *et al*. 1997; Shaw, Grenfell & Dobson 1998; Wilson *et al*. 2002; Poulin 2006)). The theory and techniques developed in the parasite aggregation literature are directly applicable to understanding and describing the nature of $V$.

### SOCIAL CONTACTS

Among the most commonly used metrics to approximate contact rates are population density and social group size. In both cases, it is assumed that individuals living in larger groups or in more dense populations experience higher rates of contact (Coté & Poulin 1995; Keeling & Rohani 2008). Indeed, higher contact rates in dense populations are a ubiquitous assumption in epidemiological models that assume density-dependent transmission (Keeling & Rohani 2008). While these metrics allow for the study of heterogeneity in contact rates between social groups and populations or across time, understanding individual-level variation in contact rates and $V$ is crucial. Recently, social network theory has gained traction as a method for quantifying variation in contact patterns at the individual level. Contact is usually quantified through direct observations of behaviour, measures of shared space use or proximity-logging collars (Croft, James & Krause 2008; Craft & Caillaud 2011), and using a network framework, each individual's level of connectivity is evaluated with established network metrics (White, Forester & Craft 2015).

Average network connectivity can also be calculated for individuals in the same age-class or species, providing a straightforward way to quantify class- or species-level heterogeneity (Rushmore *et al*. 2013; VanderWaal *et al*. 2014b). One widely used connectivity metric is 'degree,' which is the total number of individuals the focal animal is linked to in the social network (Wasserman & Faust 1994; Wey *et al*. 2008). The 'degree distribution' essentially quantifies heterogeneity in connectivity among individuals in the network. Quantifying the degree distribution has received enormous attention in the literature because it serves as a proxy for variation in $V$ if it is assumed that the number of individuals that an individual is able to infect is directly proportional to the number of animals with which it is in contact. However, caution should be exercised when using degree as a proxy for $V$, since contact rates by themselves only measure one dimension of $V$ and contact rates measured for healthy animals may not necessarily reflect interaction patterns when sick animals are present in a population (Hawley *et al*. 2011). Moreover, the definition of what type of interaction constitutes contact relevant for transmission will vary based on the biology of the focal pathogen.

### ACHIEVING A MORE HOLISTIC VIEW OF $V$

Due to the complex and interacting nature of components determining $V$, measuring infectiousness, the infectious

period, or contact rates by themselves may not yield an accurate understanding of $V$. Thus, new methods are needed for generating a more holistic understanding of $V$. Two possible ways to approach this are through expanding social network theory to include concrete measures of who transmitted to whom, and by refining approaches for modelling pathogen dynamics.

Network analysis has often been lauded as the next major tool for examining how heterogeneous transmission patterns impact disease spread (Wey *et al*. 2008; Sih, Hanser & McHugh 2009; Craft & Caillaud 2011; Godfrey 2013). Because of limitations on detecting transmission events, conclusions about disease spread in social networks are often based on the possibility that transmission *could* occur between interacting individuals (Perkins, Ferrari & Hudson 2008; Böhm, Hutchings & White 2009; Craft *et al*. 2009; Grear, Perkins & Hudson 2009; Hamede *et al*. 2009; Perkins *et al*. 2009). In a true transmission network, however, individuals are interlinked based on who transmitted to whom rather than who is in contact with whom. An individual's degree in the transmission network is by definition the total number of infections produced by that individual. When the network is defined in this way, the degree distribution becomes the distribution of $V$ with mean $R_0$. Unlike in social networks, which only identify individuals with the highest 'potential' for spreading pathogens based on their distribution of contacts, transmission networks correctly identify the individuals who are responsible for the majority of pathogen spreading. Network theory, therefore, is a useful approach for conceptualizing the combination of physiological and behavioural heterogeneity in transmission as long as who transmitted to whom can be reliably determined, though such data are rarely available.

One way to obtain data on who transmitted to whom is by using genetic data on the pathogen itself. If two individuals share genetically identical subtypes of a pathogen, then transmission can be inferred (Archie, Luikart & Ezenwa 2009; Bull, Godfrey & Gordon 2012). These data can then be used to construct a transmission network based on quantifiable transmission events (Blyton *et al*. 2014; VanderWaal *et al*. 2014a,b). The advantage of this method is that it allows the transmission network to be defined independently of the social network, allowing for the question of the extent to which heterogeneity in contact patterns determines heterogeneity in transmission patterns to be explicitly addressed. For example, individual giraffe (*Giraffe camelopardalis*) and brushtail possums (*Trichosurus cunninghami*) that were strongly linked within their social networks were more likely to be connected in transmission networks based on *Escherichia coli* strain-sharing (Blyton *et al*. 2014; VanderWaal *et al*. 2014a). In both cases, the architecture of the transmission network was determined primarily by networks derived from social interactions and not contact in space. VanderWaal *et al*. (2014a) also showed that individual giraffe with large number of connections in the social network had a higher number of transmission connections in the *E. coli* transmission network, and giraffe in bottleneck positions of the social network occupied similar positions in the transmission network. This indicates that the position of a giraffe within its social network determines, at least in part, its position in the transmission network. This work demonstrates the potential utility of an approach that combines microbial genetics with network theory for quantifying heterogeneity in transmission. Variation in transmission patterns not attributable to behaviour likely emerges from either poor definitions of contact or undersampling of individual behaviour, or more interestingly, physiological heterogeneity. Such heterogeneities are generally not measured in studies of social networks and infectious disease. However, a mismatch between patterns of contact and pathogen occurrence may help generate testable hypotheses about when and how physiological mechanisms contribute to $V$.

Other genetic approaches can also be used to assess heterogeneity in transmission, particularly at higher scales. For example, population genetic studies that focus on gene flow between pathogen metapopulations found in different classes of individuals or species (Blouin *et al*. 1995; Brown *et al*. 2008; Rwego *et al*. 2008; Archie & Ezenwa 2011; Chiyo *et al*. 2014) could be used to approximate $V$, with high gene flow indicating potential super-spreading classes or species. In rapidly evolving pathogens, phylogenetic approaches can yield valuable insights into $V$ by elucidating the evolutionary relationships among genetic lineages. These can be used to infer recent cases of interspecific transmission or non-random patterns of transmission between host populations using ancestral character state reconstruction, and in rare cases, quantify transmission between host individuals (Metzker *et al*. 2002; Biek *et al*. 2003; Goldberg 2003; Archie, Luikart & Ezenwa 2009; Ypma *et al*. 2012). In general, such methods are likely most relevant for quantifying the frequency and directionality of transmission among host species, and thus are most relevant for quantifying species-level heterogeneity.

Other marker-based approaches offer novel ways to construct transmission networks in natural settings (Naug 2008), though they do not incorporate variation in individual infectiousness. To understand potential transmission heterogeneities for white-nose syndrome in hibernating bats, UV-fluorescent dust was sprinkled on individuals at the onset of hibernation, and the spread of dust among individuals was used to approximate 'transmission' (Hoyt *et al*. 2014). As another example, specially designed DNA markers derived from a cauliflower virus have been used to track transmission events in childcare settings via contaminated objects. In this case, the spread of the DNA marker was used to emulate a faecal-orally transmitted pathogen (Jiang *et al*. 1998). Marking individual vectors, such as lice in lemurs, and longitudinally observing their occurrence on multiple hosts can also reveal host-to-host transfers of lice and, consequently, transmission potential for vector-borne diseases (Zohdy *et al*. 2012).

Finally, modelling provides an important approach for studying mechanisms that generate heterogeneity in $V$ and for exploring the population-level implications of individual heterogeneity on epidemiological processes. Models represent an opportunity to study not only the consequences of contact network structure (e.g., network modelling) (Keeling 2005; Keeling & Eames 2005; Salathé & Jones 2010; Ames *et al.* 2011; Craft & Caillaud 2011), but to also build in other sources of heterogeneity, and when empirical data on $V$ are unavailable, test how these sources theoretically contribute to $V$ by tracking the number of new infections produced by each infected individual. The concept of $V$ is highly compatible with the classic between-host Susceptible-Infected-Recovered epidemiological models, as they provide a ready platform for incorporating individual variation in contact patterns, immunity and the duration of immunological memory, mortality and recovery (Anderson & May 1991). In addition, within-host models are useful for incorporating the demographics of the pathogen within the host, such as parasite fertility, mortality, development rate and interactions with the host's immune system (Mideo, Alizon & Day 2008; Handel, Longini & Antia 2010). A union of within-host models and between-host SIR models allows questions about linkages between physiological and behavioural mechanisms to be investigated (Vickers & Osgood 2007; Mideo, Alizon & Day 2008; Garira, Mathebula & Netshikweta 2014), and $V$ to be directly assessed from model output. These immuno-epidemiological models incorporate pathogen dynamics at different biological scales, providing a means to link within-host and between-host dynamics [reviewed in (Hellriegel 2001; Mideo, Alizon & Day 2008)]. The within-host model determines the recovery, mortality and infectiousness for an individual, which then influence between-host transmission and, consequently, the number of new infected individuals resulting from the focal individual. Although still in their infancy, these multi-scale models provide a promising framework for testing hypotheses about how individual heterogeneity in physiological (within-host) and behavioural (between-host) mechanisms affect $V$ and for evaluating how heterogeneities in independent components of $V$ affect disease dynamics.

## Concluding remarks

In response to heightened interest among ecologists and epidemiologists in how individual-level factors scale up to drive population-level and higher scale processes, there has been a recent explosion of research characterizing the mechanisms that generate heterogeneities in infection. However, much of this work has focused on one component of $V$ at a time, and a more holistic understanding of the combined components of $V$ is crucial if we are to fully understand disease dynamics. Collaborations among disease ecologists, ecoimmunologists, geneticists, epidemiologists, behavioural and physiological ecologists are increasingly essential for understanding the various dimensions of the transmission process and how these relate to patterns of disease spread. We have just begun to scratch the surface on holistic approaches for quantifying $V$, and the exploration of genetic techniques for quantifying variation in $V$ and multi-scale modelling for identifying factors that contribute to variation in $V$ merits much further exploration. In addition, there are numerous complexities to be explored, such as spatiotemporal variation in $V$ during the course of an individual's lifetime or within a single epidemic. Although we are just beginning to understand the sources and significance of heterogeneity in transmission potential, we are at an exciting stage where the disparate factors affecting $V$ can begin to be assembled to enhance our understanding of infectious diseases in natural populations.

## Acknowledgements

KVW was supported by USDA-NIFA AFRI Foundational Program grant #2013-01130 and the Cooperative State Research Service, U.S. Department of Agriculture, under Project No. MINV-62-044. VOE received support from National Science Foundation Awards DEB-1102493 and IOS-1101836. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the authors and do not necessarily reflect the views of the U.S. Department of Agriculture.

## Data accessibility

This paper does not use data.

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*Received 20 September 2015; accepted 28 January 2016*
*Handling Editor: Dana Hawley*

## Supporting Information

Additional Supporting information may be found in the online version of this article:

**Fig. S1.** Number of susceptible contacts per infected individual over time in the Box 1 simulation model of disease spread